REMARKS

Claims 2 and 27 are canceled. Applicants reserve the right to pursue the canceled subject matter in one or more continuing applications. Claims 1, 3 and 26 have been amended. The amendments are supported throughout the application as filed, e.g. by original claims 1, 3 and 26; and at p. 2, lines 4-8 and lines 14-15; p.7, lines 2-4; p. 9, lines 35-36; p.13, lines 22-23.

Applicants would like to thank Examiner Tung for taking the time to conduct a telephonic interview on July 24, 2003 with Applicant's attorney. The amendments entered with this reply reflect the examiner's suggested amendments to clarify the differences between the claims and Passmore *et al.* (US 5,976,846).

Upon entry of this amendment, claims 1 and 3-26 will be pending.

Rejections under 35 U.S.C. §112, second paragraph, Indefiniteness

Claims 1 and 3-27 have been rejected for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. Claim 27 is canceled. Examiner states that the phrases "a first region", "a second region", "a first common region", and "a second common region", are vague and indefinite and that the definitions of these terms are unclear. This rejection is respectfully traversed.

MPEP §706.03(d) explains the standard for indefiniteness: "If the scope of the claimed subject matter can be determined by one of ordinary skill in the art, a rejection using paragraph 7.34.01 [the paragraph used by the examiner in this office action] is inappropriate." The meanings of "a first region" and "a second region" as used in this application (to describe portions of vectors, inserts and primers) would be readily understood by a person of ordinary skill in the art. For example, a person of ordinary skill would understand that a vector "having a first region and a second region" is a vector that has one portion or sequence, i.e. a "first region" of contiguous nucleotide molecules, that is positionally distinguishable from a second portion or sequence, i.e. "second region" of contiguous nucleotide molecules. This use of the term "region" is a term of art in the field of molecular biology generally and in the art of DNA library making in particular. The term is commonly used to denote a distinguishable "region" within any

nucleic acid, e.g. within a vector the term "region" can be used to denote a "multiple cloning region". Therefore, the term "region" is not unclear to a person of skill in the art. Moreover, the terms "first" and "second" are not technical terms. Rather, they merely describe the existence of two regions, each region distinguishable from the other.

The phrase "common" is defined throughout the specification to describe a region that is shared by each molecule in a plurality. See p. 2, line 9; p. 4, line 25; p. 6 line 39; p. 9 line 39 wherein the term is defined: "common means that each molecule of the plurality includes the common sequence." This concept, that each insert molecule in a plurality of inserts used to make a library would share a common sequence with every other insert in the plurality (i.e. the sequence is common among the plurality), is readily understood by persons of ordinary skill in the art. Many DNA library-making methods employ one or more common sequences among a plurality of inserts. Therefore, the terms "a first common region" and "a second common region" as used in this application are not indefinite, in light of the specification, to a person of skill in the art.

For the reasons indicated above applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. §102(b), Anticipation

Claims 1, 8-10, 13, 14, and 18 have been rejected as anticipated by Andersson et al. Examiner argues that because the claims have "no limitations that require to prepare the first region and the second region of the vector and the first common region and the second region of the insert," the Andersson "double adaptor" method anticipates the claims. This rejection is respectfully traversed. The presently claimed methods are novel over the Andersson method in at least two ways.

First, the plurality of inserts in the claims must have a "first common region" and "a second common region which is homologous with said first region of the vector" (emphasis added). The Andersson method, on the other hand, discloses a vector modified with adaptors to include two "5'-overhangs complementary to those on the inserts." Andersson et al., p.107

Abstract line 14-15; *see also* Figure 2. The Andersson vector overhangs and insert overhangs are reverse complementary to each other, but they are not homologous. To illustrate: The Andersson vector overhangs consist of the sequence:

5'-TGATGAACTACT-3';

The Andersson insert overhangs consist of sequence:

5'-AGTAGTTCATCA-3'

As can be seen, these two sequences are reverse complementary, i.e. they can anneal to each other, but they are not homologous, i.e., they do not have homology. Homology is both known in the art and is explicitly defined in the specification to mean "a degree of sequence identity of two DNA molecules, sufficient to allow homologous recombination between the two DNA molecules to occur" p.13 line 18-20. In contrast, the sequences disclosed in Andersson are not even minimally identical, and they would not allow homologous recombination to occur between the insert and vector. For this reason the claims are not anticipated by Andersson.

Second, the claims of the present application teach a method for making a library by "allowing homologous recombination to occur between a vector molecule" and a "nucleic acid insert molecule". The Andersson method, on the other hand, creates a library by the "annealing of insert to vector." See e.g., p.107, Abstract line 15; and p.109 first column, the paragraph headed "*Annealing of Insert to the Vector and Transformation.*" Andersson teaches the simple annealing of vector to insert *in vitro*, in a very simple buffer mixture, without the addition of any enzyme. Homologous recombination, on the other hand, is a molecular mechanism that occurs *in vivo* in the claimed methods (i.e., in the host cells). Thus, Andersson has nothing to do with homologous recombination.

In fact, the single-stranded overhangs required for the Andersson annealing method, are not suitable for homologous recombination. Homologous recombination requires a DNA strand exchange, or "cross over", between two double-stranded DNA molecules with regions of homology. A textbook published at the time of filing summarizes homologous recombination thus: "Two homologous DNA molecules 'cross over'; that is, their double helices break and the two broken ends join to their opposite partners to reform two intact double helices...." Alberts *et*

al. Molecular Biology of the Cell 3rd ed. (1994), p.263 (emphasis added); *see generally* p.325 and pp. 263-65 of Alberts (copies enclosed); *see also* the specification p. 13 lines 9-18. The Andersson method does not disclose the recombination of two double-stranded DNA molecules to produce two double-stranded molecules after a recombination event. Andersson discloses the annealing of single-stranded overhangs, to produce only one double-stranded molecule. Thus, single-stranded overhangs are not suitable for homologous recombination.

Accordingly, Andersson does not disclose vectors and inserts that share two common regions of homology, nor does Andersson disclose homologous recombination between the inserts and vectors to build a library. For the reasons presented above, applicants respectfully request that examiner withdraw this rejection.

Claim 27 has been rejected as anticipated by Passmore et al. Claim 27 is canceled. Applicants reserve the right to pursue the subject matter of this claim in one or more continuing application.

Rejections under 35 U.S.C. §103, Obviousness

Claim 7 has been rejected as obvious over Andersson et al., in further view of Passmore et al. This rejection invokes Andersson "as applied to claims 1 and 8-10, 13-14, and 18 above," (OA p.5). This rejection is respectfully traversed. Neither Andersson nor Passmore, alone or in combination, suggest the method of claim 7.

Andersson, even in view of Passmore, simply does not disclose or suggest the use of "common regions" in a plurality of inserts that are homologous to regions in the vector. As discussed above, Andersson discloses inserts and vectors that have complementary regions (i.e. the overhangs), not homologous regions. A person of ordinary skill in the art would not be motivated to modify the Andersson method to use homologous double-stranded regions instead of single-stranded complementary regions because such a modification would render the Andersson method inoperable. The MPEP makes it clear that "**[i]f the proposed modification would render the prior art invention being modified unsatisfactory for its intended**

purpose, then there is no suggestion or motivation to make the proposed modification." MPEP 2143.01 citing In re Gordon 733 F.2d 900 (Fed. Cir. 1984).

Passmore's suggested use of yeast as a host cell does not cure this defect in Andersson. Using yeast as a host cell could not produce a recombination event between the single-stranded, non-homologous overhangs disclosed by Andersson. Indeed, for the reasons discussed above, Andersson's complementary insert and vector overhangs would not recombine in any host, including yeast, because the Andersson insert and vector overhangs are neither double-stranded nor homologous. The DNA fragments taught by Andersson are simply unsuitable for building a library in the yeast host taught by Passmore.

Passmore's disclosure that yeast is a good host for homologous recombination cannot supply the appropriate motivation for modifying the Andersson method to arrive at the method of claim 7. Modifying the Andersson inserts to include regions that are homologous, instead of complementary, to regions in the vector would prevent the annealing of insert to vector, which is an integral step in the Andersson method.

For the above reasons applicants respectfully request that examiner's rejection of claim 7 be withdrawn.

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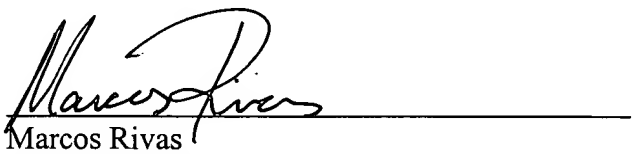
Respectfully submitted,

Date: 11-25-2003



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